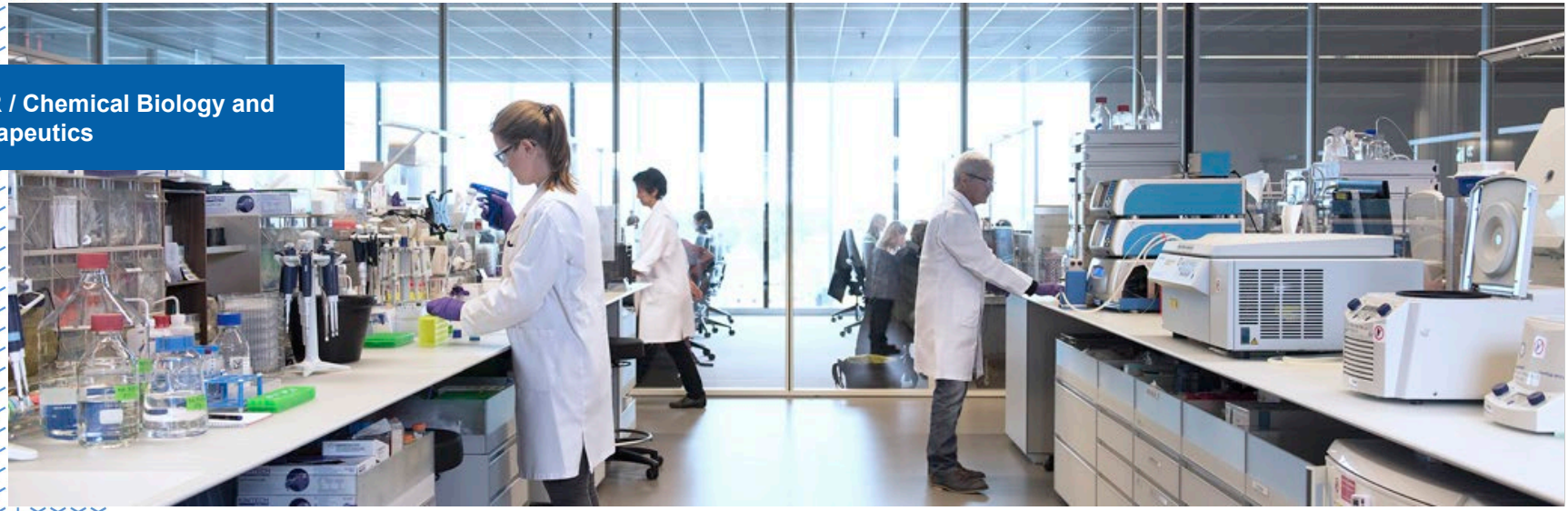
NIBR / Chemical Biology and Therapeutics



LEAPS meets Industry

Sandra Jacob, Ph.D.
Executive Director, Global Protein Sciences, CBT
Novartis Institutes for Biomedical Research

LEAPS plenary meeting, 27th October 2022

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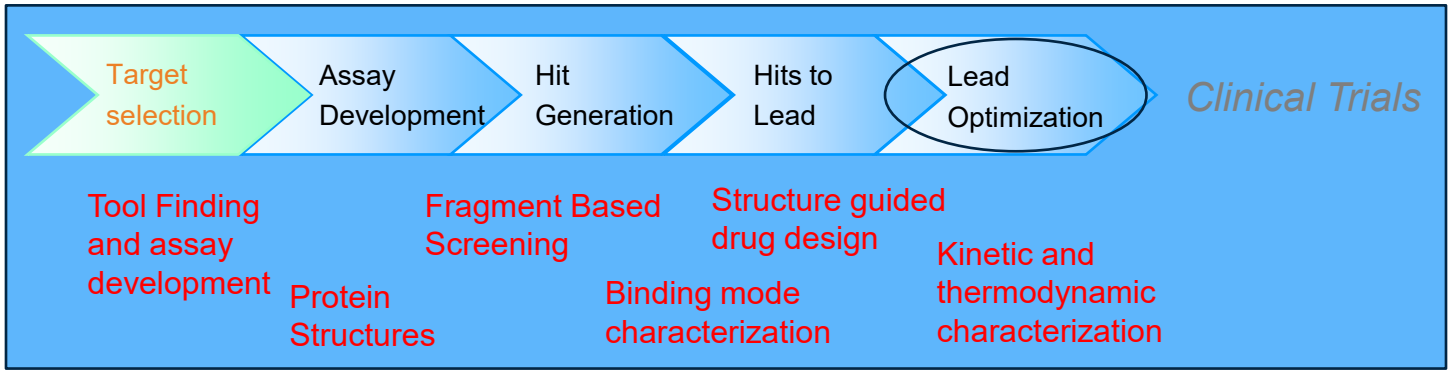
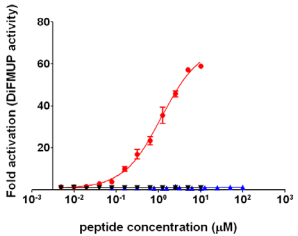
Structural Biology in Industry

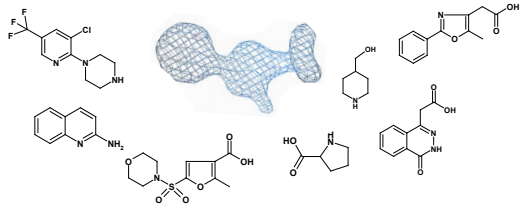
An expanding role in drug discovery



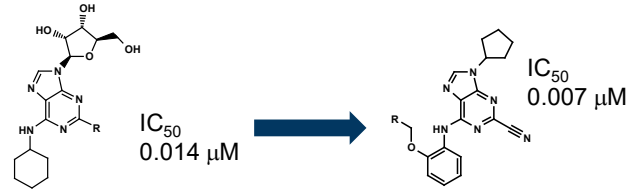
Innovative assay modalities



Fragment-based drug discovery



Hit optimization



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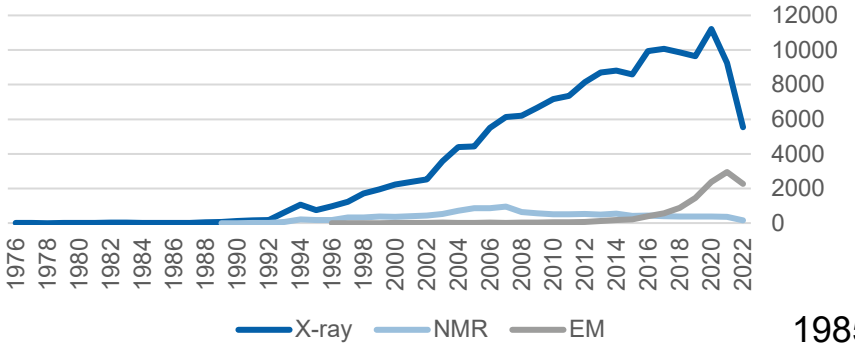
Structural biology in industry

Structures released annually in the PDB



Technical breakthroughs

Implications for Industry

1975	1985	1995	2005	2015
Isolated proteins Data collection on film	Recombinant proteins Area detectors Synchrotron sources	Cryo-cooling of crystals Dedicated synchrotron access	3rd generation synchrotrons Pixel detectors	Free Electron Lasers Cryo-EM
→ Academia	1st groups established in industry	Lead optimisation	SBDD drugs on the market	GPCRs and other IMPs enabled

Machine Learning (Alpha Fold 2)

The next era

Alphafold2, RoseTTAFold, …

"'Is there even a need for experimental structure determination anymore?', 'Is there a future career in structural biology for me?', 'Will it be possible to get tenure in this field?', 'Will funding agencies now think that structure determination is not necessary and stop funding my projects/methods development efforts?', 'Will expensive infrastructure (synchrotrons, microscopes, spectrometers) still get funded?'.

…

In summary, we are optimistic that, far from witnessing the end of structural biology, we are part of an exciting revolution in biology where structure will play a much more prominent role than in the past, at least on a par with the role that protein sequences are playing today."

Gerard J. Kleywegt & Sameer Velankar IUCr Newsletter (2022) Vol 30 (#2)

Impact of structural predictions using AI on drug discovery

Acceleration of specific scientific projects:

- Quick start for protein construct design
- Rapid determination of new structures by X-ray and EM
- Molecular understanding leading to initial ideas on potential modes of action

Experimental structures still required:

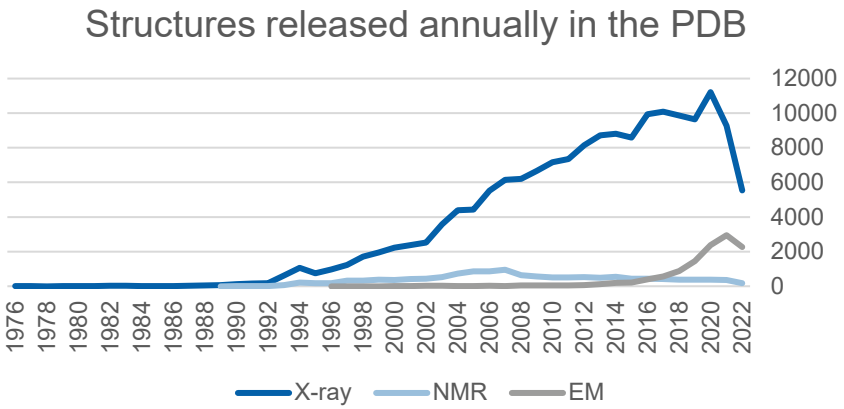
- Protein-ligand complexes
- Protein-protein or protein nucleic acid complexes
  - Still a huge gap in experimental information for RNA, which will make development of prediction algorithms difficult
- Conformational states

Contributions of Structural Biology to Drug Discovery

- PDB archival holdings facilitated discovery of ~90% of the 210 new drugs approved by the US Food and Drug Administration 2010-2016

Goodsell et al. Protein Sci (2020), 29:52-65

- All our X-ray structures are done using synchrotron sources (Novartis and other pharma companies AFAIK)
- There are many more structures per unique protein sequence done in industry compared to academia



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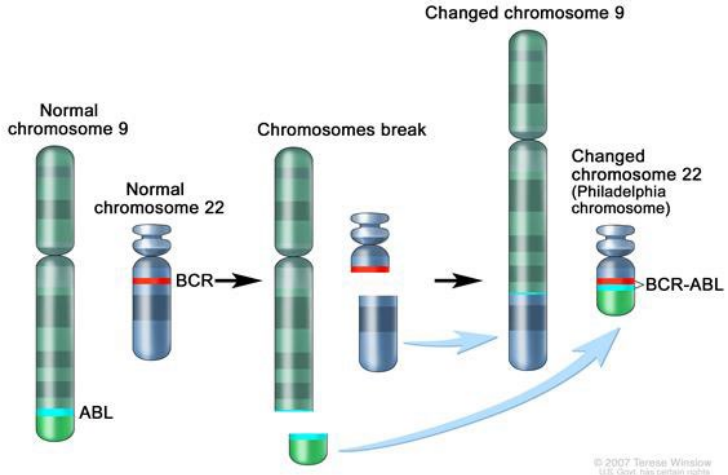
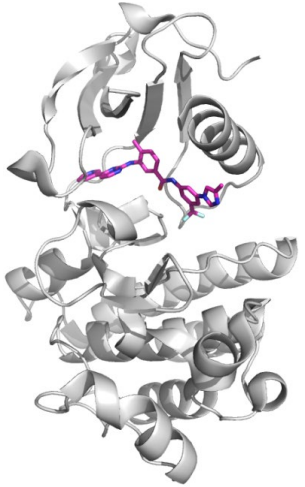
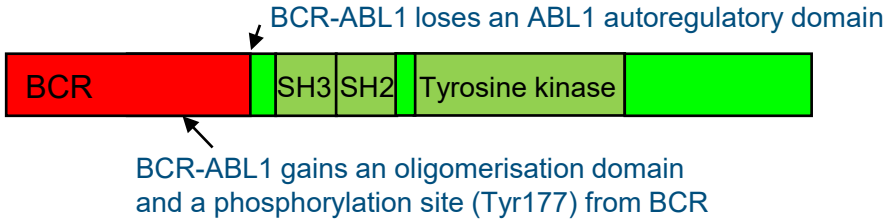
Example 1:
Abl kinase as a target for the treatment of Chronic Myelogenous Leukemia (CML)



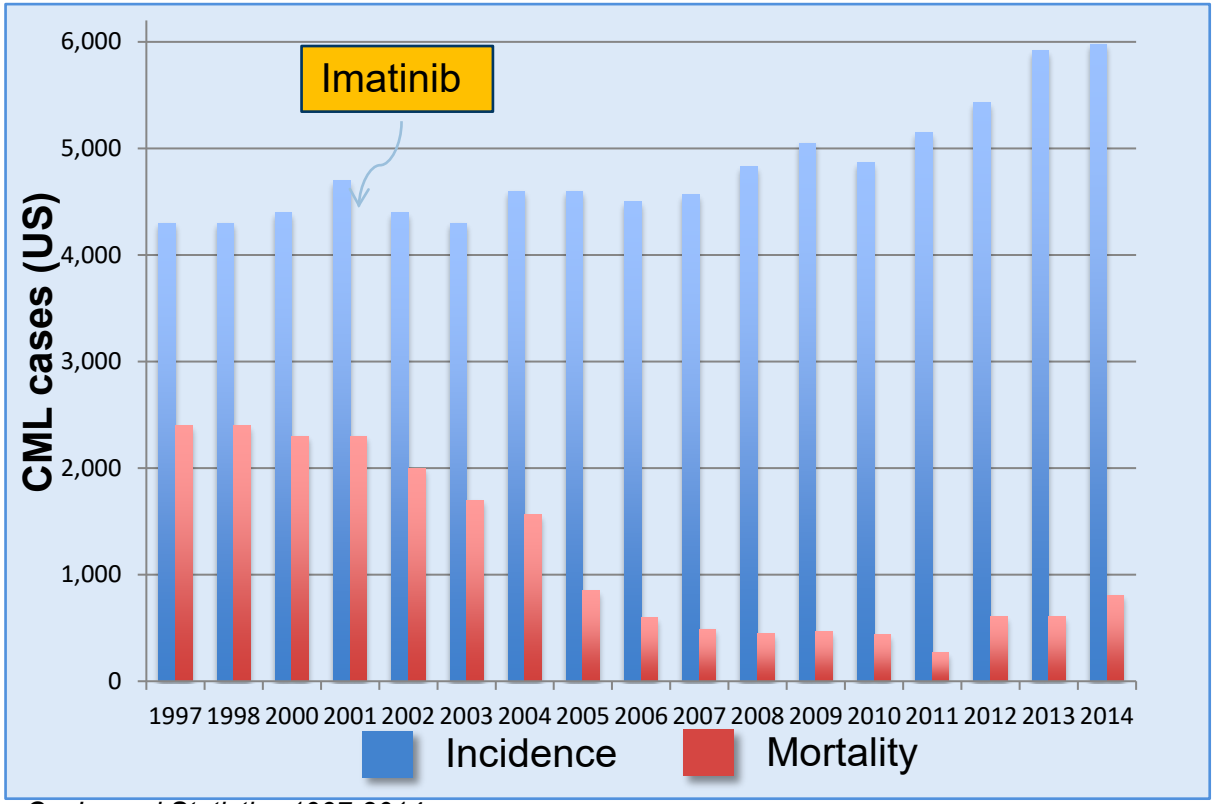
The chimeric BCR-ABL1 oncogene encodes a protein in which ABL1 kinase is constitutively activated.



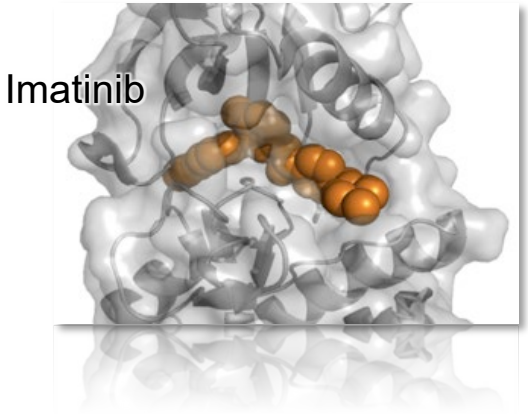


The genetic paradigm validated:

a *dramatic reduction in the mortality from CML since 2001*



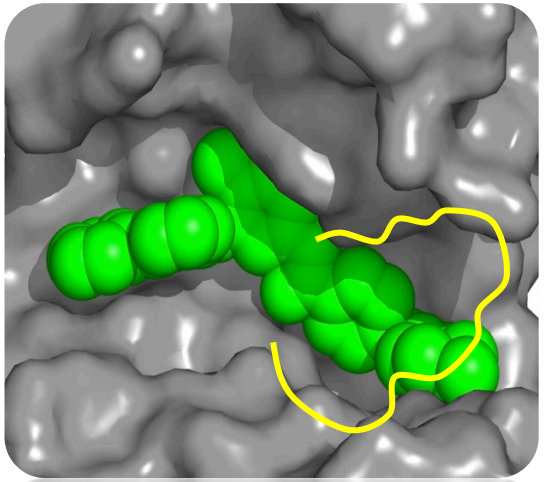
Ca Journal Statistics 1997-2014



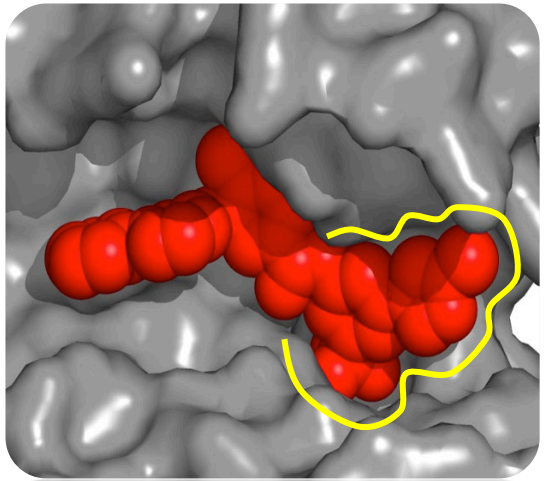
Weisberg E, Manley PW et al Cancer Cell. 2005 7:129-41

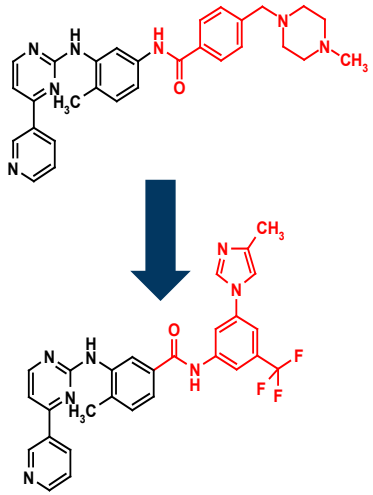
Increasing potency of ABL inhibition

Imatinib



Nilotinib



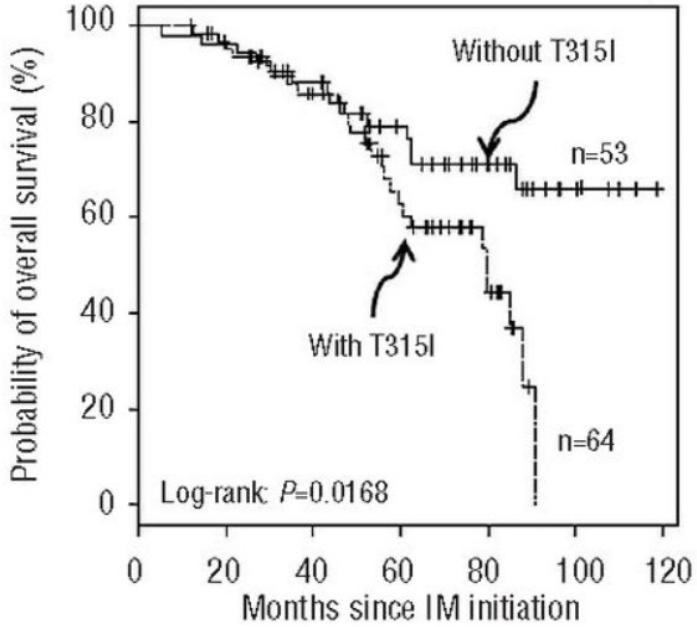


Feature	Imatinib	Nilotinib
BCR-ABL Inhibition (cell IC_{50})	221 nm	20 nm
cKIT inhibition (cell IC_{50})	108 nM	151 nM

Unmet medical need in CML

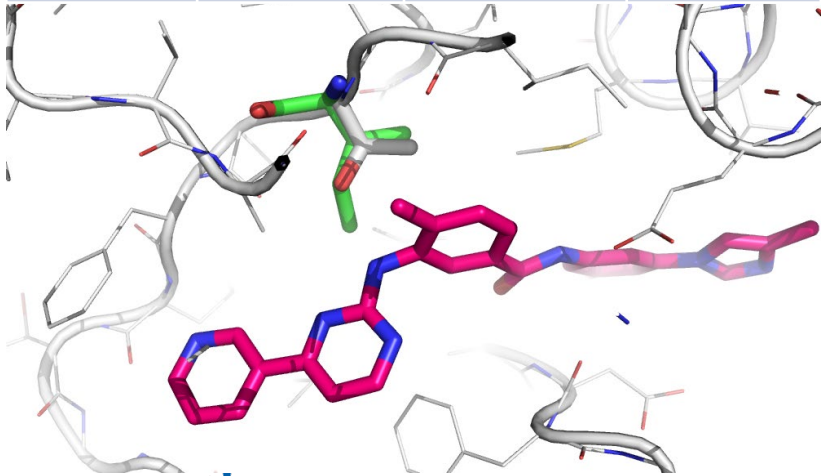
Challenges in developing T315I-selective inhibitors

Overall survival of imatinib treated CP CML patients



IC_{50} of inhibitors against BCR-ABL in BaF3

Inhibitors	BCR-ABL WT, μM	BCR-ABL T315I, μM	BaF3, μM
Imatinib	0.3	7.0	7.4
Nilotinib	0.03	4.0	> 10
Dasatinib	0.001	3.0	> 7.0



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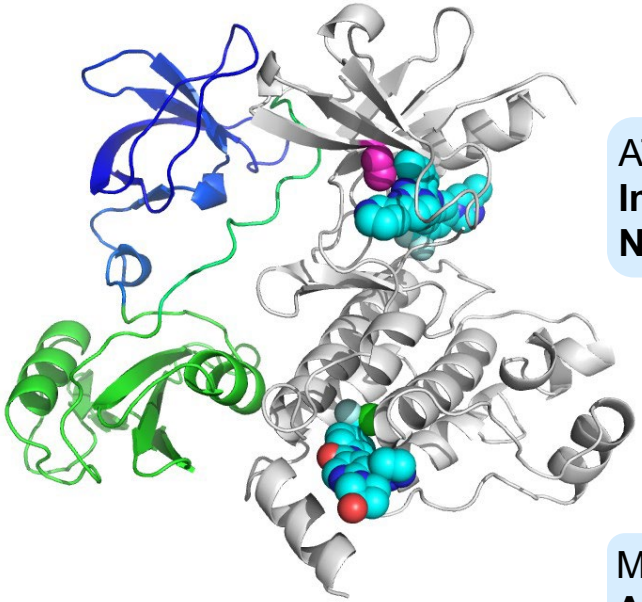
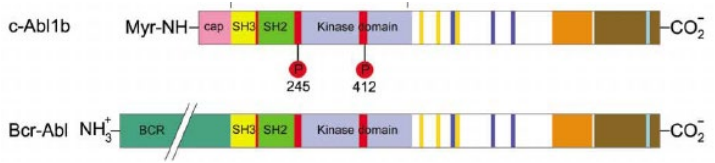
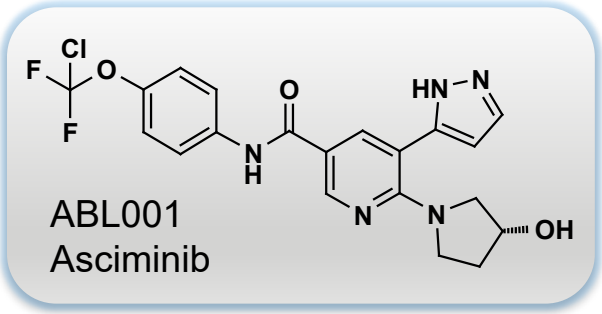
Discovery of Asciminib, an allosteric inhibitor of BCR-ABL



ATP-binding site
Imatinib
Nilotinib

Myristate binding site
Asciminib





ABL001
Asciminib

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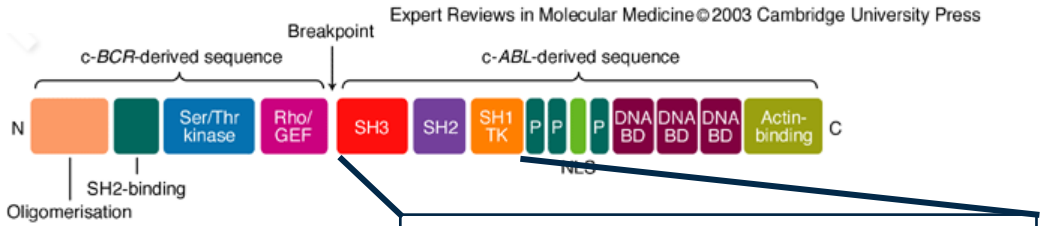
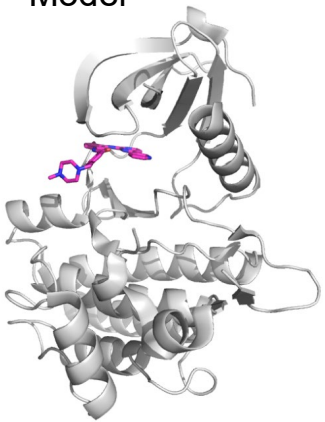
Lessons learned in SBDD for BCR-ABL inhibitors to treat CML

BCR-ABL

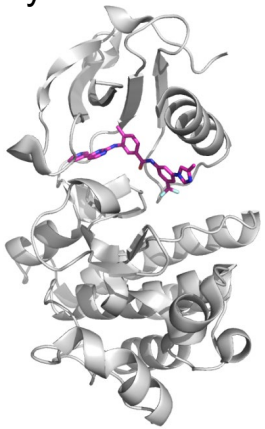


Model



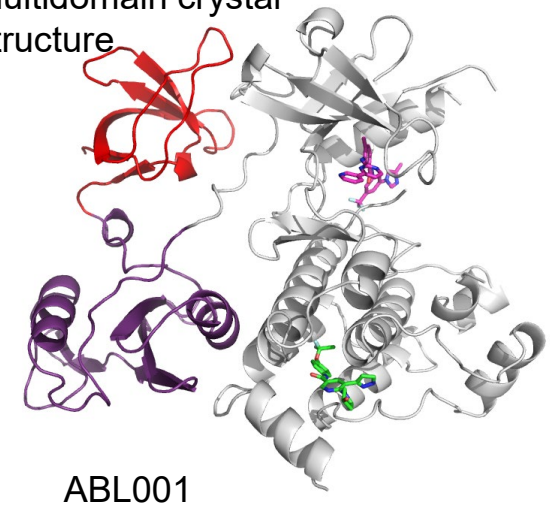
Imatinib
(Gleevec)

Crystal structure



Nilotinib
(Tasigna)

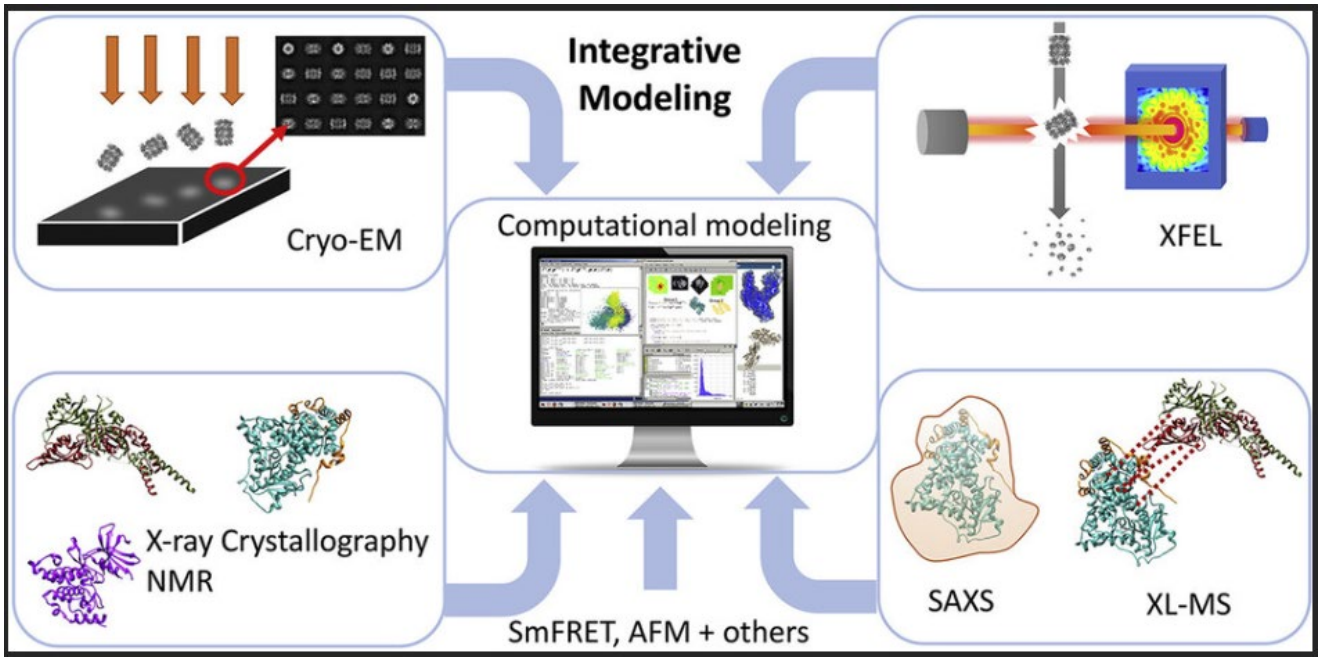
Multidomain crystal structure



ABL001
Asciminib (Scemblix)

Integrative/hybrid modelling

Integrative/Hybrid Modeling Approaches for Studying Biomolecules, Srivastava et al.
J Mol Biol, Volume 432, Issue 9, 17 April 2020, Pages 2846-2860



Example 2: Collaborating on new conronavirus antivirals

Novartis

UC Berkeley

Gates foundation

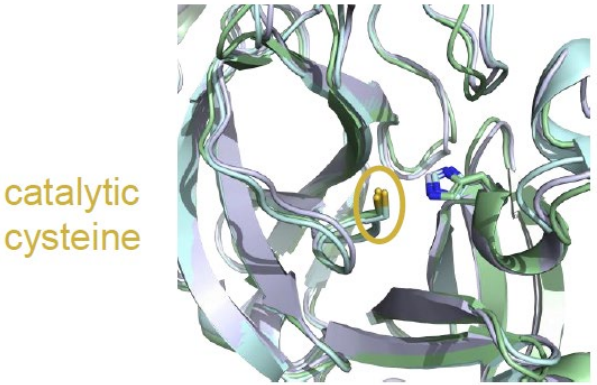
Internally:

Rapid establishment of gene-structure: first co-structures with covalent inhibitors within 2 weeks

Externally:

~500 mPro structures in the PDB

Mpro, a virally-encoded cysteine protease



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What else will impact the future of structural biology in industry?

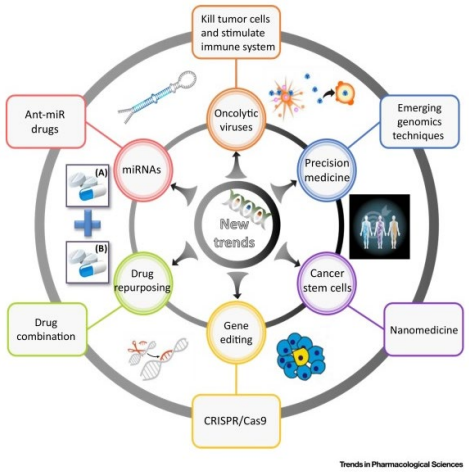
What proportion of “traditional” drug discovery will remain?

- LMW
- Biologics

And what developments will occur in these areas?

- Covalent
- Degraders
- Glues

Trends in Pharmacological Sciences, Volume 38, Issue 10, October 2017, Pages 852-872



Drugs of the future

What would be the structural contributions to emerging trends?

- Cell engineering (e.g. CAR-T)
- miRNA
- Viral systems
- Gene editing
- RLT
- Digital

Structural biology in pharmaceutical industry – trends:

Protein complexes (molecular understanding)

EM studies (especially IMPs)

Better understanding of what happens in the cell

Conformational states

Automation

Joint projects with academia

Portfolio of LMW DD projects

Conclusions:

- Structural biology still has a very important role to play in drug discovery
  - AI is not there yet for protein-ligand structure predictions
  - Synchrotron access is essential
- Need to reduce or at least maintain current baseline costs of structure determination
  - e.g. maintaining internal hardware, software
  - e.g. xFEL, via access through specialized companies or academia depending on questions asked

Thank you

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